REMARKS

Claims 39-43 and 74 are pending. Claims 1-38 and 44-73 are cancelled without prejudice as relating to a non-elected invention. Claims 41, 43 and 74 are currently amended. New claims 75-84 have been added. Support for new claims 75-84 are found throughout the specification. No new matter is added by this amendment.

Applicants thank Examiner Belyavskyi for clarifying that the priority to U.S. Provisional Application No. 60/169,082, filed December 6, 1999, U.S. Provisional Application 60/215,109, filed June 28, 2000, and U.S. Provisional Application 60/238,880, filed October 6, 2000, has been recognized.

In view of the above, Applicants submit that the effective filing date of the instant application is December 6, 1999.

Rejection of Claims 39-43 and 74 under 35 U.S.C. §102(a)

Claims 39-43 and 74 are rejected under 35 U.S.C. §102(a) for alleged lack of novelty in view of Zulewski et al. March 2001, Diabetes, 50:521.

The Office Action states at page 4 that "Zulewski et al. teach an isolated nestin-positive human pancreatic stem cell[s] that are not a neural stem cell[s] that can differentiate to form insulin-producing cells...[w]hile Zulewski et al. do not specifically teach that these cells are GLP-1R positive cells, said cells would inherently be GLP-1R-positive cells, since the cell population taught by Zulewski et al. is identical to that claimed in the instant application."

Applicants respectfully traverse the rejection.

Claim 39 claims "an isolated, nestin-positive human pancreatic or liver stem cell that is not a neural stem cell". Amended claims 43 and 74 and new claims 77-79 also relate to nestin-positive stem cells.

New claims 75 and 76 relate to a method of isolating a stem cell from the pancreas. New claim 75 claims a method of isolating a stem cell from a pancreas, comprising the steps of: (a) removing a pancreatic islet from a donor, (b) removing cells from said pancreatic islet wherein said islet comprises a plurality of cell types comprising stem cells; and (c) separating said stem cells from said plurality of cells. Support for this claim is found at page 16, lines 1-2 of the specification wherein "isolating a stem cell" is defined as "the process of removing a stem cell from a tissue sample and separating away other cells which are not stem cells of the tissue." Additional support is found at page 15, lines 3-7 wherein the specification defines a "pancreatic stem cell" as "a stem cell that has been isolated from pancreatic tissue and/or a cell that has all of the characteristics of: nestin-positive staining, nestin gene expression, GLP-1R-positive staining, GLP-1R gene expression, cytokeratin-19 negative staining, long-term proliferation in culture, and the ability to differentiate into pseudo-islets in culture."

Applicants also submit that there are both pre and post-filing publications, as well as post-filing data from the inventor's laboratory that teach the claimed method of new claim 75.

For example, attached hereto is a post-filing publication from the inventor's laboratory (Abraham et al., *2002, Endocrinology*, 143:3152, Exhibit A) wherein nestin-positive islet-derived progenitor cells are identified as follows: "islets were washed and cultured in RPMI 1640 medium containing serum, 11.1 mM glucose, antibiotics, sodium pyruvate, β-mercaptoethanol, and growth factors. Within several days, nestin-positive progenitor cells grew out from islets. These cells were cloned and expanded in medium containing 20 ng/ml each of bFGF and EGF."

Applicants have also attached a Rule 1.132 declaration of Dr. Habener stating that nestin-positive cells can be isolated by digesting islets with trypsin to prepare single cell suspensions of human pancreatic islet preparations and growing the resulting cells in an appropriate medium, for example RPMI 1640 (11 mmol/l glucose) with 10 mmol/l Hepes buffer, 1 mmol/l sodium pyruvate, 10% fetal bovine serum, 25 ng/ml EGF, 20 ng/ml bFGF and 1X penicillin/streptomycin. The resulting expansion cultures of progenitor cells contain two major

populations of cells that are phenotypically distinct cell types; those that express nestin and vimentin and those that express epithelial markers cytokeratin 19 and E-cadherin, as detected by immunofluorescence (see attached figure, Exhibit B).

The two major populations of cells are easily separated based on differences in their morphologies. The nestin/vimentin positive spindle shaped fibroblast-like cells are markedly different from that of the E-cadherin/CK19 positive, flat, cuboidal epithelial-like cells that are in patches. Under regular or phase contrast light microscopy, using low power, nestin/vimentin positive cells that are clearly separated from the E-cadherin/CK19 cells which grow in distinct patches, are selected.

Based on the forgoing, one skilled in the art will appreciate that a variety of separation strategies based on immunophenotyping methodologies such as surface coated antibody panning, fluorescent antibody tagging for physical isolation, flow cytometric sorting, immunomagnetic bead and particle selection and counterselection will be useful in carrying out the present invention. As shown herein, a number of selection criteria can be employed to allow the isolation of distinct populations of nestin+/vimentin+/cytokeratin 19-/E-cadhedrin- cells. It is also appreciated by one skilled in the art that other markers known in the field, using similar separation strategies, can be employed to isolate distinct populations of nestin+ cells.

Support for such methods is also disclosed in the instant specification which states at page 24, lines 21-25 that "[s]tem cells according to the invention can be identified by their expression of nestin or GLP-1R, or co-expression of nestin and GLP-1R by, for example, FACS, immunocytochemical staining, RT-PCR, Southern, Northern and Western blot analysis, and other such techniques of cellular identification as known to one skilled in the art." The instant specification characterizes the markers present on the stem cells of the invention (see page 30) and also discloses antibodies to stem cell markers including nestin, GLP-1R, vimentin and cytokeratin-19 (see page 25).

Support for the subject matter of claims 39, 43 and 74-79 is found in the instant application, as well as in the following priority documents: U.S. Provisional Application No. 60/169,082, filed December 6, 1999, U.S. Provisional Application 60/215,109, filed June 28, 2000, and U.S. Provisional Application 60/238,880, filed October 6, 2000. The effective filing date for claims 39, 43, and 74-79 is therefore December 6, 1999.

In view of the above, the Zulewski et al. reference is not prior art to the invention as claimed in claim 39, 43 and 74-79.

Claims 40-42 and new claims 80-84 include the limitation of an isolated, GLP-1R-positive human pancreatic or liver stem cell that is not a neural stem cell.

Applicants have attached a Rule 1.131 declaration from Dr. Habener demonstrating that the subject matter of claims 40-42 and new claims 78-84 was conceived prior to the publication of the Zulewski et al. reference.

Applicants also submit that the Zulewski et al. reference does not teach an isolated liver stem cell, or a pharmaceutical composition comprising an isolated liver stem cell, as claimed in claims 39-43, 74, 81 and 83.

In view of all of the above, Applicants submit that claims 39-43 and 74, as well as new claims 75-84 are novel in view of the Zulewski et al. reference and respectfully request reconsideration and withdrawal of the 35 U.S.C. §102(a) rejection.

Rejection of Claims 39-43 and 74 under 35 U.S.C. §102(b)

Claims 39-54 and 74 are rejected under 35 U.S.C. §102(b) for alleged lack of novelty in view of WO 97/15310 or WO 00/09666.

WO 97/15310

The Office Action states at page 5 that "WO '310 teaches an isolated nestin-positive human pancreatic stem cell[s] that are not a neural stem cell[s] that can differentiate to form insulin-producing cells...[t]he method of isolating said cells is substantially similar to that used by applicant (see overlapping pages 22-24 in particular). . . WO '310 does not specifically teach that these cells are GLP-1R positive cells, said cells would inherently be GLP-1R-positive cells, since the cell population taught by WO '310 is identical to that claimed in the instant application."

Applicants respectfully traverse the rejection.

Claims 39, 40, 43 and 74 include the limitation of "an **isolated, nestin-positive** human pancreatic or liver stem cell that is not a neural stem cell." (Emphasis added) Claims 41 and 42 include the limitation of "an **isolated, GLP-1R-positive** human pancreatic or liver stem cell that is not a neural stem cell." (Emphasis added)

The WO '310 application does not teach either "an **isolated, nestin-positive** human pancreatic or liver stem cell that is not a neural stem cell" or "an **isolated, GLP-1R-positive** human pancreatic or liver stem cell that is not a neural stem cell" as required by claims 39-43 and 74 of the instant application. (Emphasis added)

Applicants submit that the Examiner must provide rationale or evidence tending to show inherency to properly make a rejection under 35 U.S.C. 102 when the prior art is silent as to an inherent characteristic (MPEP §2112).

A "stem cell" is defined in the instant application at page 11, line 25 through page 26 line 1 as "a undifferentiated cell which is capable of essentially unlimited propagation either *in vivo* or *ex vivo* and capable of differentiation to other cell types."

A "pancreatic stem cell" is defined in the instant application at page 15, lines 3-7 as "a stem cell that has been isolated from pancreatic tissue and/or a cell that has all of the characteristics of: nestin-positive staining, nestin gene expression, GLP-1R-positive staining,

GLP-1R gene expression, cytokeratin-19 negative staining, long-term proliferation in culture, and the ability to differentiate into pseudo-islets in culture."

"Isolated" is defined in the instant application at page 16, lines 1-13 as follows:

> "Isolating" a stem cell refers to the process of removing a stem cell from a tissue sample and separating away other cells which are not stem cells of the tissue. An isolated stem cell will be generally free from contamination by other cell types and will generally have the capability of propagation and differentiation to produce mature cells of the tissue from which it was isolated. However, when dealing with a collection of stem cells, *e.g.*, a culture of stem cells, it is understood that it is practically impossible to obtain a collection of stem cells which is 100% pure. Therefore, an isolated stem cell can exist in the presence of a small fraction of other cell types which do not interfere with the utilization of the stem cell for analysis or production of other, differentiated cell types. Isolated stem cells will generally be at least 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 98%, or 99% pure. Preferably, isolated stem cells according to the invention will be at least 98% or at least 99% pure."

The instant specification teaches one embodiment of a method of isolating a nestin-positive or GLP-1R positive human pancreatic stem cell in Example 1 (see page 48, line 15 through page 49, line 27) wherein the instant specification states:

> "Rat islets were isolated from the pancreata of 2-3 month old Sprague-Dawley rats using the collagenase digestion method described by Lacy and Kostianovsky. Human islets were provided by the Diabetes Research Institute, Miami, FL using collagenase digestion. The islets were cultured for 96 hrs at 37°C in 12-well plates (Falcon 3043 plates, Becton Dickinson, Lincoln Park, NJ) that had been coated with concanavalin A. The culture medium was RPMI 1640 supplemented with 10% fetal bovine serum, 1mM sodium pyruvate, 10mM HEPES buffer, 100 μg/ml streptomycin, 100 units/ml penicillin, 0.25 μg/ml amphotericin B (GIBCO BRL, Life Science Technology, Gaithersburg, MD), and 71.5 mM β-mercaptoethanol (Sigma, St. Louis, MO).
>
> After 96 hrs, fibroblasts and other non-islet cells had adhered to the surface of concanavalin A coated wells and the islets remained floating (did not adhere to the surface). At this time, the media containing the islets were removed, centrifuged down, and the purged islets replated in 12-well plates without a coating of concanavalin A. The islets were then cultured in the above RPMI 1640 medium supplemented with 20 ng/ml of basic fibroblast growth factor-2 and 20 ng/ml of epidermal growth factor.

> The islets adhered to the surface of the plates, and cells grew out and away from the islets in a monolayer. **These cells that form a monolayer were nestin-positive by immunostaining with a rabbit anti-rat nestin antiserum** developed by Dr. Mario Vallejo at the Massachusetts General Hospital. Other nestin antibodies may be used, for example the R.401 antibody described hereinabove, or the MAB533 antibody. A monoclonal antibody specific for rat embryo spinal cord nestin, MAB353, ATCC No. 1023889; is described in Journal of Neuroscience 1996; 16:1901-100; and also available from Chemicon International, Single Oak Dr., Temecula, CA 92590 USA. **After two weeks of culture, several (3-5) of the nestin-positive monolayer cells were removed by picking with a capillary tube (cylinder cloning) and were replated** on the 12-well plates (not coated with concanavalin A) and cultured in the RPMI 1640 medium further supplemented with bFGF-2 and EGF. The cells propagated at a rapid rate and reached confluence after six days of culture. After 12 days of culture, the cell monolayer formed waves in which they begin to pile up in a co-linear manner. On day 15 of culture, the cell waves began to condense, migrate into spheroid bodies and by day 17 the surface of the wells contained these spheroid bodies (ca. 100 μm in diameter), empty spaces, and a few areas of remaining monolayer cells. Several of these monolayer cells were re-picked and re-cloned and the process described above occurred again in precisely the same temporal sequence." (Emphasis added)

Additional embodiments of methods of isolating a nestin-positive or GLP-1R positive human pancreatic stem cells are discussed hereinabove in the section addressing the rejection of claims 39-43 and 74 in view of Zulewski et al., incorporated herein in its entirety, as well as in the attached Rule 1.132 declaration of Dr. Habener.

The invention of the WO '310 application "concerns the discovery that functional islets containing insulin-producing β-cells, as well as other islet cell types, can be grown in long-term cultures from pluripotent stem cells, which give rise to islet producing stem cells, IPSCs" (see page 8, lines 27-30). The WO '310 application discloses at page 12, lines 21-23 that "IPSCs are a small population of cells derived from ductal epithelial cells (i.e., these cells are pancreas-derived but are not differentiated islet cells)".

The WO '310 application teaches a method of growing IPSCs at page 13 line 29 through page 14, line 25 wherein it is stated that,

> " [t]he method of the subject invention involves making suspensions of cells, including stem cells, from the pancreas of a mammal. . .The cell suspensions are prepared using standard techniques. The cell suspension is then cultured in a nutrient medium that facilitates the growth of the IPSCs, while at the same time severely compromising the sustained growth of the differentiated or mature cells other than IPSCs. . . What is required for such media is that they have little or no glucose (less than about 1 mM) and low serum (less than about 0.5%). The high amino acid concentrations are preferably of amino acids known to be essential for the cells of the species being cultured, and provide a carbon source for the cultured cells. In addition, at least one rudimentary lipid precursor, preferably pyruvate, is provided. These conditions are so stressful to most differentiated cell types that they do not survive. Surprisingly, however, upon extended culture of cells from pancreatic tissue without re-feeding (about 3 weeks) IPSCs do survive and after extended culture, begin to proliferate."

The Examiner asserts that the method of isolating cells that is described in the WO '310 application (in particular at pages 22-24) is "substantially similar" to the method of isolating cells described in the instant application. The WO '310 application discloses a method of growing IPSCs at pages 22-24. However, the method of growing IPSCs presented in the WO '310 application (see pages 13-14 and 22-24) does not include a step wherein nestin-positive or GLP-1R positive human pancreatic stem cells are isolated. The WO '310 application therefore teaches "suspensions of cells, including stem cells, from pancreas of a mammal" (page 13, lines 29-30) and a method of growing islet producing stem cells (IPSCs) but does not teach an **isolated nestin-positive or GLP-1R positive** human pancreatic stem cell that is not a neural stem cell, as required by claims 39-43 and 74 of the instant application.

The WO'310 application does not disclose the percent purity of the IPSCs that are grown according to the disclosed method. The attached Rule 1.132 declaration of Dr. Habener asserts that the percentage of nestin-positive cells in the pancreas is believed to be in the range of 0.2 to 5 %. Given the very low percentage of nestin-positive stem cells in the pancreas, one of skill in the art would not accept that the method of growing stem cells presented in the WO '310 application would result in an isolated nestin-positive or GLP-1R positive pancreatic stem cell as required by claims 39-43 and 74 of the instant application, since this method lacks a step wherein nestin-positive or GLP-1R positive stem cells are isolated. In view of the above, Applicants

respectfully assert that one of skill in the art would not accept that the suspension of stem cells grown according to the method described in the WO '310 application is an isolated nestin-positive or GLP-1R positive human pancreatic stem cell as required by instant claims 39-43 and 74, and as defined in the instant application.

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) ...; *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. **Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.**' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (Emphasis) (MPEP §2112, citations omitted).

In view of the above, one of skill in the art would not accept that "an isolated, nestin-positive human pancreatic or liver stem cell that is not a neural cell" or "an isolated, GLP-1R positive human pancreatic or liver stem cell that is not a neural stem cell" as required by claims 39-43 and 74 of the instant application would inherently be identical to the suspension of stem cells grown according to the methods of the WO '310 application since, given the small percentage of nestin-positive and GLP-1R positive cells in the pancreas, and due to the absence of a step wherein nestin-positive or GLP-1R positive human pancreatic stem cells are isolated, it is unlikely that the cells of the WO '310 application are **isolated** nestin-positive or GLP-1R positive human pancreatic stem cell as defined by the instant application (that is, at least 30% pure).

One of skill in the art would also not accept that it is necessarily probable or possible that the suspension of stem cells grown according to the methods of the WO '310 application are inherently "an isolated, nestin-positive human pancreatic or liver stem cell that is not a neural

stem cell" or "an isolated, GLP-1R-positive human pancreatic or liver stem cell that is not a neural stem cell" as required by claims 39-43 and 74 of the instant application.

Applicants respectfully submit that the Examiner has not provided extrinsic evidence that makes clear that "the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill". That is, the Examiner's assertion that "the cell population taught by WO '310 is identical to that claimed in the instant application" is based on mere probabilities and possibilities.

Applicants submit further that the WO '301 application does not teach an isolated liver stem cell, or a pharmaceutical composition comprising an isolated liver stem cell, as claimed in claims 39-43, 74, 81 and 83.

WO 00/09666

The Office Action states at page 5 that "WO '666 teaches an isolated nestin-positive human pancreatic stem cell[s] that are not a neural stem cell[s] that can differentiate to form insulin producing cells. WO '666 teaches that said cells is also GLP-1R positive cells..."

Applicants respectfully traverse the rejection.

The WO 00/09666 publication states at page 13, lines 28-31, "[n]on-insulin producing cells, including primary acinar cells, acinar cell lines (e.g., AR42J), and stem cells, that were not previously thought to have GLP-1 receptors and not previously thought to be capable of producing insulin can respond to GLP-1 and Exendin-4..." However, this publication does not teach an isolated, nestin-positive human pancreatic or liver stem cell that is not a neural cell, as claimed in claims 39, 43, or 74, a method of isolating a stem cell from a pancreas, and a stem cell isolated by this method, as claimed in new claims 75-79, or, an isolated GLP-1R-positive human pancreatic or liver stem cell that is not a neural stem cell, as claimed in claims 40-42 and new claims 80-84.

The instant application defines a "pancreatic stem cell" at page 15, lines 3-8 as "a stem cell that has been isolated from pancreatic tissue and/or a cell that has all of the characteristics of: nestin-positive staining, nestin gene expression, GLP-1R positive staining, GLP-1R gene expression, cytokeratin-19 negative staining, long-term proliferation in culture, and the ability to differentiate into pseudo-islets in culture." The instant specification also defines a "liver stem cell" at page 15, lines 8-10 as "a stem cell that has been isolated from liver tissue and/or a cell that has all of the characteristics of: nestin-positive staining, nestin gene expression and long-term proliferation in culture." As discussed above, the instant specification also discloses methods for isolating a stem cell of the invention.

Although the WO 00/09666 publication describes a stem cell at page 15, lines 5-6, as including "pancreatic stem cells and non-pancreatic stem cells that have been promoted to produce IDX-1, Beta2/NeuroD, and E47", this publication does not describe a pancreatic or liver stem cell as defined in the instant application, and does not teach how to isolate a pancreatic stem cell. In particular, the WO 00/09666 does not teach an isolated nestin-positive and/or GLP-1R positive pancreatic or liver stem cell that is not a neural stem cell.

The only working examples in the WO 00/09666 publication that teach the use of cells are limited to the AR42J cell line (an acinar cell line) (See Examples 4 and 5). As indicated on page 1, lines 30-31, of the 'WO '666 publication, acinar cells produce exocrine enzymes and are therefore distinct from stem cells taught in the instant application.

One of skill in the art would not expect that an acinar cell (for example an AR42J cell) is identical to an isolated nestin-positive and/or GLP-1R positive human pancreatic or liver stem cell that is not a neural stem cell, as claimed in claims 39-43, 74 and new claims 75-84 of the instant application.

Applicants submit that for a determination of anticipation to be proper, the prior art reference must disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO, Incorporated et al.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Neither of the WO 97/15310 reference or the WO 00/09666 reference teach an isolated, nestin-positive human pancreatic or liver stem cell that is not a neural stem cell, as claimed in claims 39, 43, 74 or 77-79 of the instant application; an isolated, GLP-1R-positive human pancreatic or liver stem cell that is not a neural stem cell, as claimed in claim 40, 41, 42 and 80-84 of the instant application; and a method of isolating a stem cell from a pancreas, comprising the steps of: (a) removing a pancreatic islet from a donor, (b) removing cells from said pancreatic islet wherein said islet comprises a plurality of cell types comprising stem cells; and (c) separating said stem cells from said plurality of cells, as claimed in claims 75-76 of the instant application.

In view of all of the above, Applicants submit that claims 39-43, 74 and new claims 75-84 are novel in view of WO 97/15310 and WO 00/009666, and respectfully request reconsideration and withdrawal of the 35 U.S.C. §102(b) rejection of claims 39-43 and 74.

Rejection of Claims 39-43 and 74 under 35 U.S.C. §102(e)

Claims 39-43 and 74 are rejected under 35 U.S.C. §102(e) for alleged lack of novelty in view of WO 01/39784 or WO 02/086107.

WO 01/39784

The Office Action states at page 6 that "WO '784 teaches an isolated nestin-positive human pancreatic stem cell[s] that are not a neural stem cell[s] that can differentiate to form insulin-producing cells...[t]he method of isolating said cells is substantially similar to that used by applicant (see overlapping pages 22-24 in particular). . . WO '784 does not specifically teach that these cells are GLP-1R positive cells, said cells would inherently be GLP-1R-positive cells, since the cell population taught by WO '784 is identical to that claimed in the instant application."

Applicants respectfully traverse the rejection.

35 U.S.C. 103(c) states that "[s]ubject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person."

The MPEP states in section 706.02(l)(1) at page 700-50, "[e]ffective November 29, 1999, subject matter which was prior art under former 35 U.S.C. 103 via 35 U.S.C. 102(e) is now disqualified as prior art against the claimed invention if that subject matter and the claimed invention 'were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person'".

As indicated in the attached statement, the inventors of the WO 01/39784 reference and the inventors of the instant application were, at the time each of the inventions were made, subject to an obligation of assignment to the same person.

In view of the common ownership of the WO 01/39784 reference and the instant application, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 39-43 and 74 under 35 U.S.C. §102(e).

WO 02/086107

The Office Action states at page 6 that "WO '107 teaches an isolated nestin-positive human pancreatic stem cell[s] that are not a neural stem cell[s] that can differentiate to form insulin producing cells...while WO '107 does not specifically teach that these cells are GLP-1R positive, said cells would inherently be GLP-1R positive since the cell population taught by WO '107 is identical to that claimed in the instant application"

Applicants respectfully traverse the rejection.

The WO 02/086107 publication teaches differentiation of stem cells, wherein the stem cells are preferably ES or EG cells (see page 5, lines 4-5 wherein the WO '107 publication states that "[t]he present invention is aimed at inducing the differentiation of ES cells by activation of specific genes into insulin-producing cells"; page 8, lines 25-27, " 'cultivation medium' means a suitable medium capable of supporting growth and differentiation of stem cells, preferably ES and EG cells.") The WO 02/086107 also discloses a method of differentiating ES cells into insulin-producing cells using culture conditions that favor the formation of nestin-positive cells (see Example 8, page 27 through 28) as well as a method of selecting nestin-positive cells from embryoid bodies (see page 13, lines 11-17). This publication does not teach a method of isolating a stem cell from a pancreas as claimed in claims 75-76 of the instant application. Further, the WO 02/086107 publication does not teach an isolated, nestin-positive human pancreatic or liver stem cell that is not a neural cell, as claimed in claims 39, 43, 74 and new claims 77-79 or, an isolated GLP-1R-positive human pancreatic or liver stem cell that is not a neural stem cell, as claimed in claim 40, amended claim 41, claim 42 and new claims 80-84.

Applicants submit that for a determination of anticipation to be proper, the prior art reference must disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO, Incorporated et al.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

The WO 02/086107 reference does not teach an isolated, nestin-positive human pancreatic or liver stem cell that is not a neural stem cell, as claimed in claims 39, 43, 74 or 77-79 of the instant application; an isolated, GLP-1R-positive human pancreatic or liver stem cell that is not a neural stem cell, as claimed in claim 40, 41, 42 and 80-84 of the instant application; and a method of isolating a stem cell from a pancreas, comprising the steps of: (a) removing a pancreatic islet from a donor, (b) removing cells from said pancreatic islet wherein said islet comprises a plurality of cell types comprising stem cells; and (c) separating said stem cells from said plurality of cells, as claimed in claims 75-76 of the instant application.

In view of all of the above, Applicants submit that claims 39-43, 74 as well as new claims 75-84 are novel in WO 01/39784 and WO 02/086107, and respectfully request reconsideration and withdrawal of the 35 U.S.C. §102(e) rejection of claims 39-43 and 74.

CONCLUSION

Applicants submit that in view of all of the above, all claims are allowable as written and respectfully request early favorable action by the Examiner.

Respectfully submitted,

Date: June 21, 2004

Name: Kathleen M. Williams
Registration No.: 34,380
Customer No.: 29933
Palmer & Dodge LLP
111 Huntington Avenue
Boston, MA 02199-7613
Tel: 617-239-0100